Docket No. 239612US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Kouji HATTORI, et al. GAU:

SERIAL NO: NEW APPLICATION EXAMINER:

FILED: HEREWITH

FOR: AMINOALCOHOL DERIVATIVES

REQUEST FOR PRIORITY

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

☐ Full benefit of the filing date of U.S. Application Serial Number , filed , is claimed pursuant to the provisions of **35 U.S.C. §120.**

☐ Full benefit of the filing date(s) of U.S. Provisional Application(s) is claimed pursuant to the provisions of **35 U.S.C. §119(e):** **Application No.** **Date Filed**

■ Applicants claim any right to priority from any earlier filed applications to which they may be entitled pursuant to the provisions of **35 U.S.C. §119**, as noted below.

In the matter of the above-identified application for patent, notice is hereby given that the applicants claim as priority:

COUNTRY	APPLICATION NUMBER	MONTH/DAY/YEAR
Australia	PS3241	June 27, 2002
Australia	2002953604	December 30, 2002

Certified copies of the corresponding Convention Application(s)

■ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

☐ were filed in prior application Serial No. filed

☐ were submitted to the International Bureau in PCT Application Number
Receipt of the certified copies by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

☐ (A) Application Serial No.(s) were filed in prior application Serial No. filed ; and

☐ (B) Application Serial No.(s)

☐ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

Respectfully Submitted,

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Patent Office
Canberra

I, JONNE YABSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PS 3241 for a patent by FUJISAWA PHARMACEUTICAL CO. and LTD. as filed on 27 June 2002.

WITNESS my hand this
Twenty-ninth day of May 2003

JONNE YABSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Aminoalcohol Derivatives"

The invention is described in the following statement:

DESCRIPTION

AMINOALCOHOL DERIVATIVES

FIELD OF THE INVENTION

This invention relates to new aminoalcohol derivatives and salts thereof which are beta-3 (β_3) adrenergic receptor agonists and useful as a medicament.

BACKGROUND OF THE INVENTION

International Publication No. WO 90/06299, published June 14, 1990, describes derivatives of phenylethanolamines as having an effect on the metabolism, preferably reduction of the blood sugar level and body fat.

DISCLOSURE OF THE INVENTION

This invention relates to new aminoalcohol derivatives which are β_3 adrenergic receptor agonists and salts thereof.

More particularly, it relates to new aminoalcohol derivatives and salts thereof which have gut sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence, anti-pollakiuria activities, anti-diabetes and anti-obesity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method of using the same therapeutically in the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in a human being or an animal.

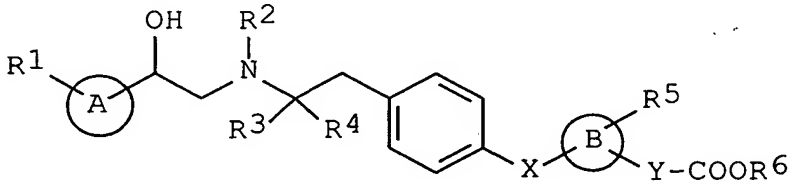
One object of this invention is to provide new and useful aminoalcohol derivatives and salts thereof which have gut sympathomimetic, anti-ulcerous, lipolytic, anti-urinary incontinence, anti-pollakiuria activities, anti-diabetes and anti-obesity.

Another object of this invention is to provide processes for the preparation of said aminoalcohol derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said aminoacohol derivatives and salts thereof.

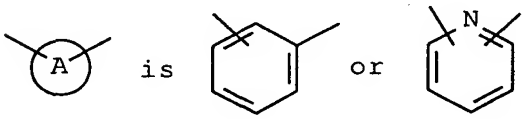
Still further object of this invention is to provide a therapeutical method for the treatment and/or prevention of aforesaid diseases in a human being or an animal, using said aminoalcohol derivatives and salts thereof.

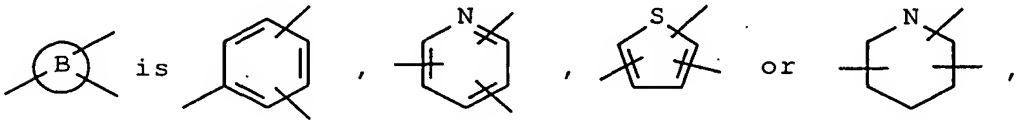
The object aminoalcohol derivatives of this invention are new and can be represented by compound of the following formula [I]:



[I]

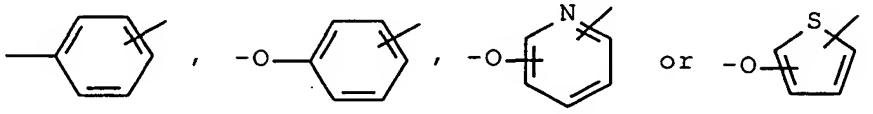
wherein





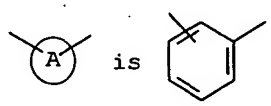
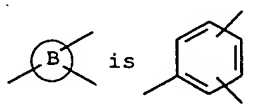
X is bond, -O-, $-OCH_2-$, -S- or $-\underset{\underset{R^7}{|}}{N}-$ (in which R^7 is hydrogen or lower alkyl),

Y is bond, $-O-(CH_2)_n-$ (in which n is 1, 2, 3 or 4), $-(CH_2)_m-$ (in which m is 1, 2, 3 or 4),



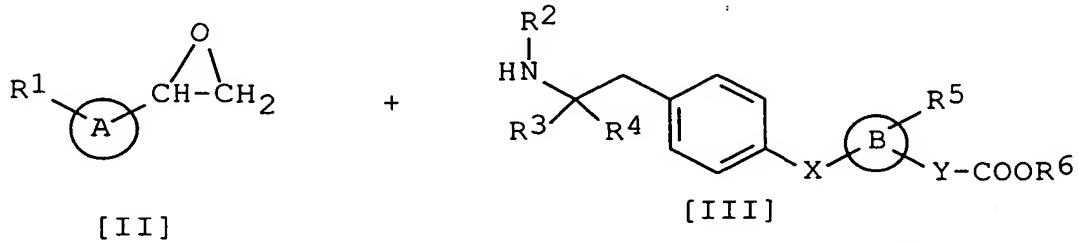
R^1 is hydrogen or halogen,

R^2 is hydrogen or an amino protective group,

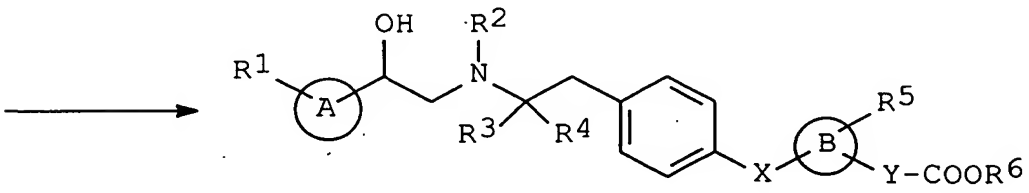
R^3 is hydrogen or lower alkyl,
R^4 is hydrogen or lower alkyl,
R^5 is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono(or di)(lower)alkylamino, mono(or di or tri)halo(lower)alkyl, cyano or phenyl, and
R^6 is hydrogen or lower alkyl,
provided that when X is bond,  and  ,
then R^5 is not hydrogen,
or a salt thereof.

According to this invention, the object compounds can be prepared by processes which are illustrated in the following schemes.

Process 1

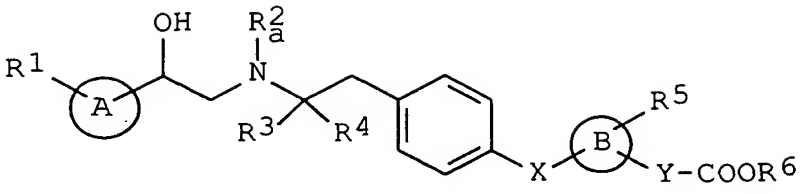


[II] [III]
or a salt thereof



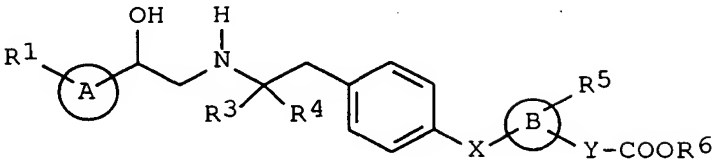
[I]
or a salt thereof

Process 2



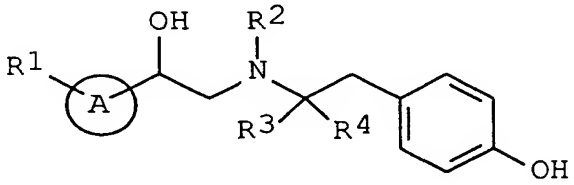
[Ia]
or a salt thereof

elimination reaction of the amino protective group



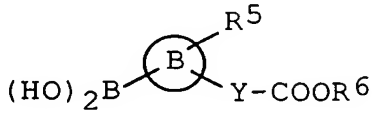
[Ib]
or a salt thereof

Process 3

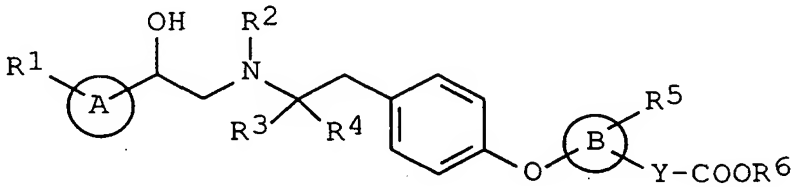


[IV]
or a salt thereof

+

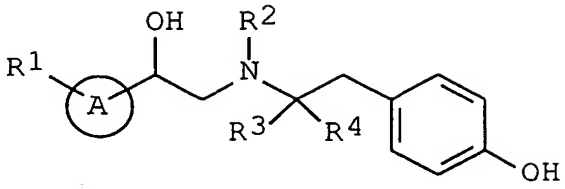


[V]
or a salt thereof



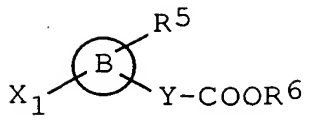
[Ic]
or a salt thereof

Process 4

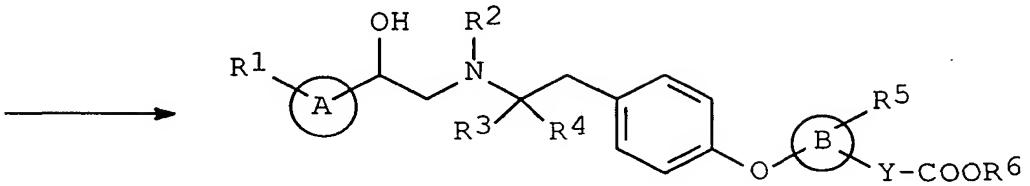


[IV]
or a salt thereof

+

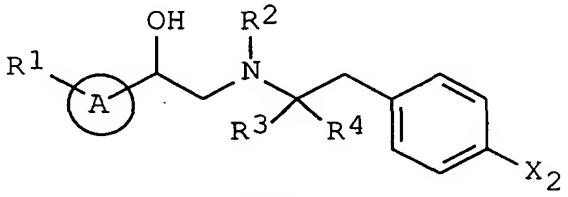


[VI]
or a salt thereof



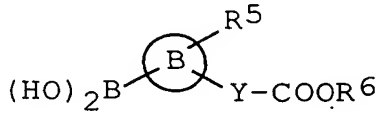
[Ic]
or a salt thereof

Process 5

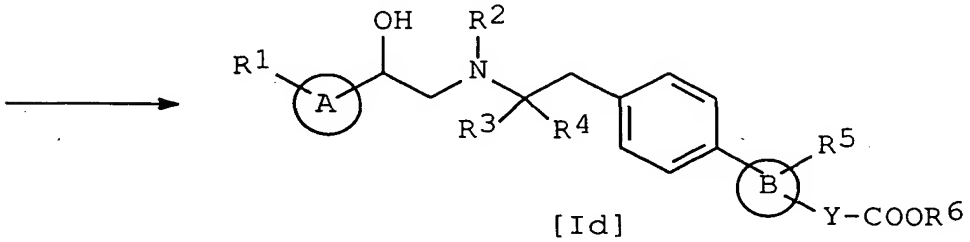


[VII]
or a salt thereof

+



[V]
or a salt thereof



[Id]
or a salt thereof

wherein  ,  , X, Y, R^1, R^2, R^3, R^4, R^5 and R^6 are each as defined above,

R_a^2 is an amino protective group, and
X_1 and X_2 are each a leaving group.

As to the starting compounds [II], [III], [Ia], [IV], [V], [VI] and [VII], some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned below or a conventional manner.

In the above and subsequent description of the present specification, suitable examples of the various definition to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" and "lower alkyl" moiety in the terms of "mono(or di)(lower)alkylamino" and "mono(or di or tri)halo(lower)alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-methylpentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and the like.

Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, tert-butoxy, pentyloxy, tert-pentyloxy, hexyloxy and the like, in which preferable one is methoxy or ethoxy.

Suitable "halogen" may be fluoro, chloro, bromo and iodo, in which preferable one is chloro.

Suitable "mono(or di or tri)halo(lower)alkyl" may include chloromethyl, dichloromethyl, trichloromethyl,

bromomethyl, dibromomethyl, tribromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1 or 2-chloroethyl, 1 or 2-bromoethyl, 1 or 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl and the like.

Suitable "leaving group" may include hydroxy, reactive group derived from hydroxy and the like.

Suitable "reactive group derived from hydroxy" may include acid residue and the like.

Suitable "acid residue" may include halogen (e.g. fluoro, chloro, bromo, iodo), acyloxy (e.g. acetoxy, tosyloxy, mesyloxy, trifluoromethanesulfonyloxy, etc.) and the like.

Suitable example of "amino protective group" moiety may be common amino protective group such as substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower alkoxycarbonyl [e.g. tert-butoxycarbonyl, tert-amyloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, ar(lower)alkyl [e.g. trityl, benzyl, etc.], and the like, in which preferable one is tert-butoxycarbonyl.

Suitable salts of the object aminoalcohol derivative [I] are pharmaceutically acceptable salts and include conventional non-toxic salts such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, oxalate, maleate, fumarate, tartrate, citrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc., an alkali metal salt [e.g. sodium salt, potassium salt, etc.] or the like.

The Processes 1 to 5 for preparing the object compounds of the present invention are explained in detail in the following.

Process 1

The object compound [I] or a salt thereof can be prepared by reacting a compound [II] with a compound [III] or a salt thereof.

Suitable salt of the compound [III] may be the same as those exemplified for the compound [I].

The reaction is preferably carried out in the presence of a base such as an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkaline earth metal carbonate [e.g. magnesium carbonate, calcium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], picoline or the like.

The reaction is usually carried out in a conventional solvent, such as an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], diethyl ether, tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 2

The object compound [Ib] or a salt thereof can be prepared by subjecting a compound [Ia] or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compounds [Ia] and [Ib] may be the same as those exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Example 11 mentioned below.

Process 3

The object compound [Ic] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [V] or a salt thereof.

Suitable salts of the compounds [Ic], [IV] and [V] may be the same as those exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Example 15 mentioned below.

Process 4

The object compound [Ic] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [VI] or a salt thereof.

Suitable salts of the compound [Ic], [IV] and [VI] may be the same as those exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Example 9 mentioned below.

Process 5

The object compound [Id] or a salt thereof can be prepared by reacting a compound [VII] or a salt thereof with a compound [V] or a salt thereof.

Suitable salts of the compounds [Id], [VII] and [V] may be the same as those exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Example 7 mentioned below.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like, and converted to the desired salt in conventional manners, if necessary.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture

thereof are included within the scope of this invention.

It is further to be noted that isomerization or rearrangement of the object compound [I] may occur due to the effect of the light, acid base or the like, and the compound obtained as the result of said isomerization or rearrangement if also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound [I] (e.g. hydrate, etc.) and any form of the crystal of the compound [I] are included within the scope of the present invention.

The object compound [I] or a salt thereof possesses gut sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities, and are useful for the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in human beings or animals, and more parcitularly for the treatment and/or prevention of spasm or hyperanakinesia in case of irritable bowel syndrome, gastritis, gastric ulcer, duodenal ulcer, enteritis, cholecystopathy, cholantitis, urinary calculus and the like; for the treatment and/or prevention of ulcer such as gastric ulcer, duodenal ulcer, peptic ulcer, ulcer causes by non steroidal anti-inflammatory drags, or the like; for the treatment and/or prevention of dysuria such as pollakiuria, urinary incontinence or the like in case of nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis, prostatic hypertrophy or the like; for the treatment and/or prevention of pancreatitis, obesity, diabetes, glycosuria, hyperlipidemia, hypertension, atherosclerosis, glaucoma, melancholia, depression or the like; for the treatment and/or prevention of diseases as the result of insulin resistance (e.g. hypertension,

hyperinsulinemia, etc.); for the treatment and/or prevention of neurogenetic inflammation; and for reducing a wasting condition, and the like.

Additionally, β_3 adrenergic receptor agonists are known to lower triglyceride and cholesterol levels and to raise high density lipoprotein levels in mammals (US Patent No. 5,451,677). Accordingly, the object compound [I] in useful in the treatment and/or prevention of conditions such as hyper-triglyceridaemia, hypercholesterolaemia and in lowering high density lipoprotein levels as well as in the treatment of atherosclerotic and cardiovascular diseases and relates conditions.

Moreover, the object compound [I] is useful for inhibiting uterine contractions, preventing premature labor, and treating and preventing dysmenorrhea.

In order to show the usefulness of the compound [I] for the prophylactic and therapeutic treatment of above-mentioned disease in human being or animals, a representative compound of the compound [I] was tested on the following pharmaceutical test.

Test

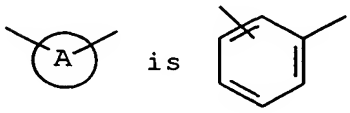
Effect on the increase in intravesical pressure induced by carbachol in anesthetized dog

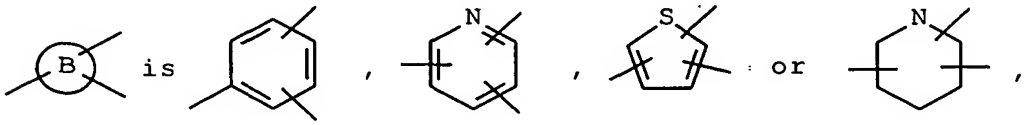
Test Method and Test Result

Female Beagle dogs weighing 8.0-15.0 kg were fasted for 24 hours and maintained under halothane anesthesia. A 12F Foley catheter was lubricated with water soluble jelly, inserted into the urethral orifice and advanced approximately 10 cm until the balloon tip was placed well inside the bladder. The balloon was then inflated with 5 ml of room air and catheter slowly withdrawn just part the

first resistance that is felt at the bladder neck. Urine was completely drained out through the catheter, and 30 ml of biological saline was infused. The catheter was connected to pressure transducer, and intravesical pressure was continuously recorder. Intravenous administration of the test compound inhibited carbachol (1.8 μl/kg)-induced increase in intravesical pressure (IVP).

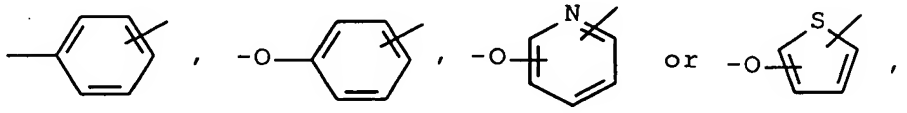
Preferred embodiments of the object compound [I] are as follows:





X is bond, -O-, $-OCH_2-$, -S- or  (in which R^7 is hydrogen or lower alkyl (more preferably C_1-C_4, most preferably methyl)),

Y is bond, $-O-(CH_2)_n-$ (in which n is 1, 2, 3 or 4), $-(CH_2)_m-$ (in which m is 1, 2, 3 or 4),



R^1 is hydrogen or halogen (more preferably chloro),

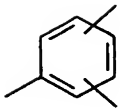
R^2 is hydrogen,

R^3 is hydrogen,

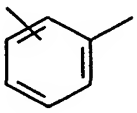
R^4 is hydrogen,

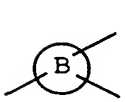
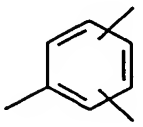
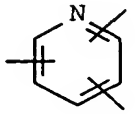
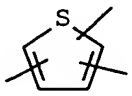
R^5 is hydrogen, halogen (more preferably chloro), hydroxy or lower alkyl (more preferably C_1-C_4, most preferably methyl), and

R^6 is hydrogen,

provided that when X is bond, and  is  ,
then R^5 is not hydrogen.

More preferred embodiments of the object compound [I] are as follows:

 is  ,

 is  ,  , or  ,

X is bond, -O-, $-OCH_2-$, -S- or $-\underset{\underset{R^7}{|}}{N}-$ (in which R^7 is hydrogen or lower alkyl (more preferably C_1-C_4, most preferably methyl)),

Y is bond, $-O-(CH_2)_n-$ (in which n is 1 or 2) or $-(CH_2)_m-$ (in which m is 1 or 2),

R^1 is hydrogen or halogen (more preferably chloro),

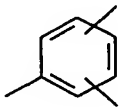
R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

R^5 is hydrogen, halogen (more preferably chloro), hydroxy or lower alkyl (more preferably C_1-C_4, most preferably methyl), and

R^6 is hydrogen,

provided that when X is bond, and  is  ,
then R^5 is not hydrogen.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

A solution of N-benzyl-2-(4-bromophenyl)ethanamine

(13.5 g) in ethanol (270 ml) was added (2R)-2-(3-chlorophenyl)oxirane (8.63 g) and the solution was refluxed for 48 hours. After cooling to room temperature, the solvent was removed by evaporation and the residue was chromatographed on silica gel (eluent: hexane/ethyl acetate = 9/1) to give (1R)-2-[benzyl[2-(4-bromophenyl)ethyl]amino]-1-(3-chlorophenyl)ethanol (18.6 g) as a colorless oil.

NMR ($CDCl_3$, δ): 2.58 (1H, dd, J=10, 13Hz), 2.68-2.89 (5H, m), 3.56 (1H, d, J=13Hz), 3.92 (1H, d, J=13Hz), 4.59 (1H, dd, J=3.4, 10Hz), 6.97 (2H, d, J=8.3Hz), 7.21-7.40 (12H, m)

(+)ESI-MS (m/z): 444 and 446 (MH^+)

Preparation 2

To a solution of (1R)-2-[benzyl[2-(4-bromophenyl)ethyl]amino]-1-(3-chlorophenyl)ethanol (18.5 g) in N,N-dimethylformamide (40 ml) were successively added imidazole (3.96 g) and tert-butyldimethylsilyl chloride (7.52 g) and the solution was stirred at room temperature for 14 hours. The reaction mixture was quenched by the addition of water (100 ml) and extracted with ethyl acetate (100 ml x 1). The extract was washed with water (100 ml x 2), brine (100 ml x 1), and dried over magnesium sulfate. Filtration followed by evaporation gave a colorless oil, which was chromatographed on silica gel (eluent: hexane/ethyl acetate) to give (2R)-N-benzyl-N-[2-(4-bromophenyl)ethyl]-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethanamine (21.0 g) as a colorless oil.

NMR ($CDCl_3$, δ): 0.15 (6H, s), 1.01 (9H, s), 2.72-2.82 (5H, m), 2.92 (1H, dd, J=5.9, 13Hz), 3.75 (1H, d, J=13.7Hz), 3.86 (1H, d, J=13.7Hz), 4.71 (1H, t-like, J=6.2Hz), 7.01 (2H, d, J=8.3Hz), 7.26-7.47 (9H, m), 7.48 (2H, d, J=8.3Hz)

(+)ESI-MS (m/z): 558 and 560 (MH^+)

Preparation 3

To a solution of tert-butyl [2-(4-bromophenyl)ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (500 mg) in 1,2-dimethoxyethane (6 ml) was added 5-formyl-2-thiopheneboronic acid (206 mg), tetrakis(triphenylphosphine)palladium (63 mg) and aqueous solution of sodium carbonate (2M, 1.0 ml), and the mixture was stirred at 80°C for 7 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydrxyethyl][2-[4-(5-formyl-2-thienyl)phenyl]ethyl]carbamate (187 mg).

(+)ESI-MS (m/z): 508 $(M+Na)^+$

Preparation 4

To a suspension of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (710 mg), 4-[[tert-butyl(dimethyl)silyl]oxy]phenylboronic acid (457 mg), triethylamine (1.26 ml) and powdered 4Å molecular sieves (700 mg) in dichloromethane (18 ml) was added copper(II) acetate (330 mg), and the mixture was stirred at room temperature for 18 hours under ambient atmosphere. The resulting slurry was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tert-butyl [2-[4-[4-[[tert-butyl(dimethyl)-silyl]oxy]phenoxy]phenyl]ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (600 mg).

(-)ESI-MS (m/z): 569 $(M-H)^-$

Preparation 5

The following compounds were obtained according to a

similar manner to that of Preparation 4.

(1) tert-Butyl [2-[4-[[4-[[tert-butyl(dimethyl)silyl]oxy]-phenyl]amino]phenyl]ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate
(+)ESI-MS (m/z): 597 $(M+H)^+$

(2) tert-Butyl [2-[4-[[4-[[tert-butyl(dimethyl)silyl]oxy]-phenyl](methyl)amino]phenyl]ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate
(+)ESI-MS (m/z): 611 $(M+H)^+$

Preparation 6

To a solution of tert-butyl [2-(4-aminophenyl)-ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (1.75 g) and formaldehyde (37% w/w solution in water, 390 µl) in 1,2-dichloroethane (20 ml) was added sodium triacetoxyborohydride (1.23 g), and the mixture was stirred at room temperature for 18 hours under nitrogen atmosphere. The resulting mixture was poured into a mixture of 1N sodium hydroxide and chloroform, and the mixture was stirred for 20 minutes. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-(methylamino)phenyl]ethyl]carbamate (550 mg).
(+)ESI-MS (m/z): 405 $(M+H)^+$

Preparation 7

To a suspension of 2-[4-[(4-methoxyphenyl)thio]phenyl]-ethanamine (6.3 g) in methanol (45 ml) and tetrahydrofuran (10 ml) was added ethyl trifluoroacetate (2.89 ml), and the mixture was stirred at room temperature for 1 hour. The mixture was evaporated under reduced pressure. The residue

was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]ethyl]acetamide (3.95 g).

(+)ESI-MS (m/z): 378 $(M+Na)^+$

Preparation 8

Under nitrogen at 4°C, to a solution of 2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]ethyl]-acetamide (1.5 g) in dichloromethane (15 ml) was added 1M boron tribromide in dichloromethane (10.5 ml), and the mixture was stirred at room temperature for 15 hours. The mixture was evaporated under reduced pressure. The residue was dissolved in a mixture of dichloromethane and saturated aqueous sodium bicarbonate. After separation, the organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give 2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]acetamide (1.42 g).

(+)ESI-MS (m/z): 364 $(M+Na)^+$

Preparation 9

To a solution of 2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]acetamide (480 mg) in methanol (5.0 ml) was added 1N sodium hydroxide solution (2.8 ml). The mixture was refluxed for 12 hours. The mixture was evaporated under reduced pressure. The residue was dissolved in a mixture of dichloromethane (40 ml), 1N hydrochloric acid solution (2.0 ml) and water (15 ml). After separation, the organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give 4-[[4-(2-aminoethyl)phenyl]thio]phenol (300 mg).

(-)ESI-MS (m/z): 244 $(M-H)^-$

Preparation 10

4-[[4-(2-Aminoethyl)phenyl]thio]phenol (295 mg) and (2R)-2-(3-chlorophenyl)oxirane (186 mg) in ethanol (3.5 ml)

was refluxed for 6 hours. The mixture was evaporated. The residue was purified by column chromatography on silica gel (chloroform/methanol = 100/3) to give 4-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]thio]phenol (155 mg).

(+)ESI-MS (m/z): 400 $(M+H)^+$

The object compound above was protected at the imino group in a conventional manner to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(4-hydroxyphenyl)-thio]phenyl]ethyl]carbamate (200 mg).

(+)ESI-MS (m/z): 500 $(M+H)^+$

Preparation 11

The following compounds were obtained according to a similar manner to that of Preparation 10.

(1R)-2-[[2-(4-Bromophenyl)ethyl]amino]-1-(3-chlorophenyl)ethanol

(+)ESI-MS (m/z): 354 $(M+H)^+$

tert-Butyl [2-(4-bromophenyl)ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate

(+)ESI-MS (m/z): 454 $(M+H)^+$

Example 1

To a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-(5-formyl-2-thienyl)phenyl]ethyl]-carbamate (180 mg) in acetonitrile (2 ml) and pH 4 buffer solution (sodium dihydrogenphosphate) (1 ml) was added 30% hydrogen peroxide solution (30 µl) and 80% sodium chlorite (67 mg) below 10°C. The reaction mixture was stirred at 50°C for 3 hours. The mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 5-[4-

[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-2-thiophenecarboxylic acid (160 mg).

(-)ESI-MS (m/z): 500 $(M-H)^-$

Example 2

The following compounds were obtained according to a similar manner to that of Example 4.

(1) 5-[4-[2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]-2-thiophenecarboxylic acid hydrochloride

NMR (DMSO-d_6, δ): 3.00-3.25 (6H, m), 4.95-4.99 (1H, m), 6.34 (1H, br), 7.33-7.47 (6H, m), 7.55 (1H, d, J=3.9Hz), 7.70-7.81 (3H, m), 9.05 (1H, br)

(-)ESI-MS (m/z): 400 $(M-HCl-H)^-$

(2) [4-[[4-[2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]amino]phenoxy]acetic acid hydrochloride

NMR (DMSO-d_6, δ): 2.84-3.30 (6H, m), 4.39 (1H, br), 4.59 (2H, s), 4.97-5.03 (1H, m), 6.37 (1H, br), 6.80-7.07 (8H, m), 7.34-7.48 (4H, m), 8.85 (1H, br), 9.11 (1H, br)

(-)ESI-MS (m/z): 439 $(M-HCl-H)^-$

(3) [4-[[4-[2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl](methyl)amino]phenoxy]acetic acid hydrochloride

NMR (DMSO-d_6, δ): 2.85-3.23 (6H, m), 3.17 (3H, s), 3.89-4.15 (1H, br), 4.65 (2H, s), 4.98-5.02 (1H, m), 6.68-7.08 (8H, m), 7.34-7.46 (4H, m), 8.86 (1H, br), 9.14 (1H, br)

(-)ESI-MS (m/z): 453 $(M-HCl-H)^-$

(4) [4-[[4-[2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]thio]phenoxy]acetic acid hydrochloride

NMR (DMSO-d_6, δ): 2.94-3.33 (6H, m), 4.70 (2H, s), 4.97-5.01 (1H, m), 6.34 (1H, br), 6.96 (2H, d, J=8.7Hz), 7.02-7.23 (4H, m), 7.33-7.45 (6H, m), 8.97-9.18 (1H, br)

(-)ESI-MS (m/z): 456 $(M-HCl-H)^-$

Example 3

To a solution of tert-butyl [2-[4-[4-[[tert-butyl(dimethyl)silyl]oxy]phenoxy]phenyl]ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (370 mg) in tetrahydrofuran (4.0 ml) was added 1M tetrabutylammonium fluoride in tetrahydrofuran (1.2 ml), and the mixture was stirred at room temperature for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a phenol product. To a solution of the product and potassium carbonate (94 mg) in N,N-dimethylformamide (4.0 ml) was added tert-butyl bromoacetate (133 mg), and the mixture was stirred at room temperature for 5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tert-butyl [4-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]phenoxy]-acetate (360 mg).

(-)ESI-MS (m/z): 597 $(M-H)^-$

Example 4

A solution of tert-butyl [4-[4-[2-[(tert-

butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenoxy]phenoxy]acetate (305 mg) and 4N hydrochloride in 1,4-dioxane (5.0 ml) was stirred at room temperature for 24 hours. The resulting solid was collected by filtration and dried to give [4-[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]phenoxy]-acetic acid hydrochloride (220 mg) as a white solid.

NMR (DMSO-d_6, δ): 2.95-3.33 (6H, m), 4.65 (2H, s), 4.99-5.04 (1H, m), 6.35 (1H, br), 6.83-7.00 (6H, m), 7.23 (9H, d, J=8.5Hz), 7.39-7.47 (4H, m), 8.98-9.12 (1H, br)

(+)ESI-MS (m/z): 442 $(M-HCl+H)^+$

Example 5

To a suspension of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (550 mg), (4-methoxycarbonylphenyl)boronic acid (300 mg), triethylamine (1.0 ml) and powdered 4Å molecular sieves (600 mg) in dichloromethane (8 ml) was added copper(II) acetate (255 mg), and the mixture was stirred at room temperature for 18 hours under ambient atmosphere. The resulting slurry was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 4-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]benzoate (185 mg).

(+)ESI-MS (m/z): 526 $(M+H)^+$

Example 6

To a solution of methyl 4-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]benzoate (183 mg) in ethanol (1.2 ml) was added 1N aqueous sodium hydroxide solution (0.6 ml), and the mixture was stirred at 40°C for 3

hours. The solvent was removed by evaporation, and the aqueous solution was acidified with 1N aqueous hydrochloride solution and extracted with ethyl acetate (30 ml x 2). The combined organic layers were washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a benzoic acid product. To a solution of the product in tetrahydrofuran (2.0 ml) was added 4N hydrochloride in 1,4-dioxane (1.0 ml), and the mixture was stirred at room temperature for 12 hours. The resulting solid was collected by filtration and dried to give 4-[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenoxy]benzoic acid hydrochloride (127 mg).

NMR (DMSO-d_6, δ): 3.00-3.28 (6H, m), 4.99-5.04 (1H, m), 6.35 (1H, br), 6.97-7.12 (4H, m), 7.32-7.48 (6H, m), 7.90-7.98 (2H, m), 9.03-9.35 (1H, br)

(-)ESI-MS (m/z): 410 $(M-HCl-H)^-$

Example 7

To a solution of tert-butyl [2-(4-bromophenyl)ethyl]-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (400 mg) in 1,2-dimethoxyethane (6 ml) was added (4-methoxycarbonyl-2-methylphenyl)boronic acid (171 mg), tetrakis(triphenylphosphine)palladium (55 mg) and aqueous solution of sodium carbonate (2M, 0.92 ml), and the mixture was stirred at 80°C for 2 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 4'-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]-2-methyl-1,1'-biphenyl-4-carboxylate (320 mg).

(+)ESI-MS (m/z): 524 $(M+H)^+$

Example 8

The following compounds were obtained according to a similar manner to that of Example 6.

(1) 5-Chloro-6-[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]nicotinic acid hydrochloride

NMR (DMSO-d_6, δ): 3.04-3.32 (6H, m), 5.03-5.07 (1H, m), 5.14 (1H, br), 7.18 (2H, d, J=8.5Hz), 7.33-7.48 (6H, m), 8.38 (1H, d, J=2.0Hz), 8.54 (1H, d, J=2.0Hz), 9.00 (1H, br), 9.35 (1H, br)

(-)ESI-MS (m/z): 445 $(M-HCl-H)^-$

(2) 4'-[2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d_6, δ): 2.28 (1H, s), 3.01-3.27 (6H, m), 5.00-5.04 (1H, m), 6.36 (1H, br), 7.28-7.48 (9H, m), 7.79-7.90 (2H, m), 9.02 (1H, br)

(-)ESI-MS (m/z): 408 $(M-HCl-H)^-$

Example 9

To a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (600 mg) and potassium carbonate (254 mg) in dimethylsulfoxide (6.0 ml) was added methyl 5,6-dichloro-3-pyridinecarboxylate (347 mg), and the mixture was stirred at room temperature for 12 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 6-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]-5-chloronicotinate (770 mg).

(+)ESI-MS (m/z): 561 $(M+H)^+$

Example 10

Under nitrogen at 5°C, to a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (1.5 g), ethyl [3-(hydroxymethyl)phenoxy]acetate (885 mg) and triphenyl phosphine (1.1 g) in tetrahydrofuran (30 ml) was added diethyl azodicarboxylate (0.66 ml). The mixture was stirred at room temperature for 12 hours and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give ethyl [3-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]methyl]-phenoxy]acetate (1.04 g).

(+)ESI-MS (m/z): 585 $(M+H)^+$

Example 11

To a solution of ethyl [3-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenoxy]methyl]phenoxy]acetate (1.0 g) in tetrahydrofuran (5.0 ml) was added 4N hydrochloride in dioxane (4.3 ml). The mixture was stirred at room temperature for 8 hours and evaporated under reduced pressure. The residue was diluted with ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol/chloroform = 1/20) to give ethyl [3-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]-methyl]phenoxy]acetate (632 mg).

(+)ESI-MS (m/z): 484 $(M+H)^+$

The object compound above was hydrolyzed in a conventional manner to give sodium [3-[[4-[2-[[(2R)-2-(3-

chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]methyl]-phenoxy]acetate (492 mg).

NMR (DMSO-d_6, δ): 2.56-2.73 (6H, m), 4.09 (2H, s), 4.58-4.64 (1H, m), 4.98 (2H, s), 6.72-6.77 (1H, m), 6.85-6.91 (4H, m), 7.08 (2H, d, J=8.5Hz), 7.17-7.26 (4H, m), 7.38 (1H, s)

(-)ESI-MS (m/z): 454 $(M-Na-H)^-$

Example 12

The following compounds were obtained according to a similar manner to that of Example 3.

(1) tert-Butyl [4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-phenoxy]acetate

(+)ESI-MS (m/z): 597 $(M+H)^+$

(2) tert-Butyl [4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-(methyl)amino]phenoxy]acetate

(+)ESI-MS (m/z): 611 $(M+H)^+$

Example 13

To a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]-carbamate (195 mg) and potassium carbonate (59 mg) in N,N-dimethylformamide (3 ml) was added tert-butyl bromoacetate (84 mg), and the mixture was stirred at room temperature for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give tert-butyl [4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]thio]-

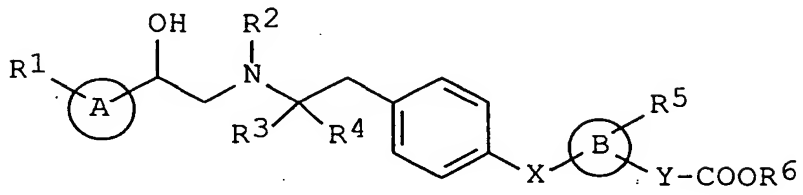
phenoxy]acetate (168 mg).

(+)ESI-MS (m/z): 636 $(M+Na)^+$

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

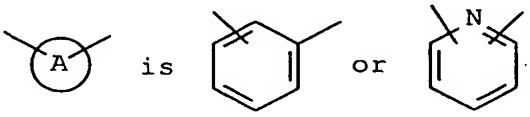
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

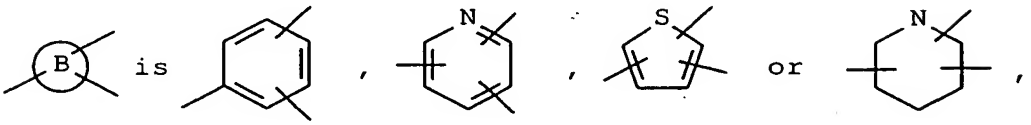
1. A compound of the formula [I]:



[I]

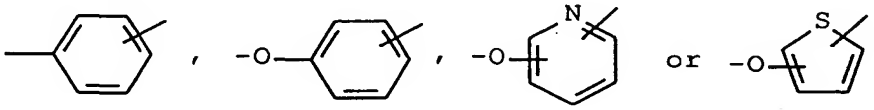
wherein





X is bond, -O-, $-OCH_2-$, -S- or $-\underset{\underset{R^7}{|}}{N}-$ (in which R^7 is hydrogen or lower alkyl),

Y is bond, $-O-(CH_2)_n-$ (in which n is 1, 2, 3 or 4), $-(CH_2)_m-$ (in which m is 1, 2, 3 or 4),



R^1 is hydrogen or halogen,

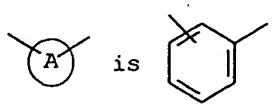
R^2 is hydrogen or an amino protective group,

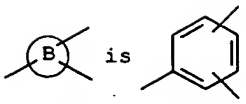
R^3 is hydrogen or lower alkyl,

R^4 is hydrogen or lower alkyl,

R^5 is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono(or di)(lower)alkylamino, mono(or di or tri)halo(lower)alkyl, cyano or phenyl, and

R^6 is hydrogen or lower alkyl,

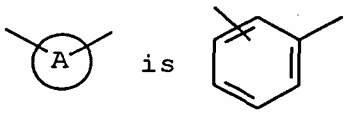
provided that when X is bond,  and

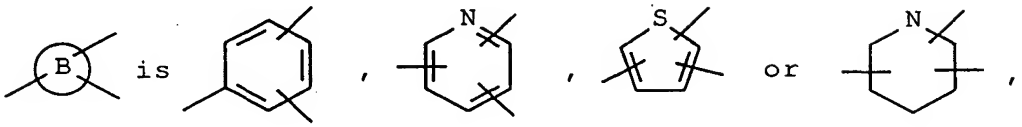


then R^5 is not hydrogen,

or a salt thereof.

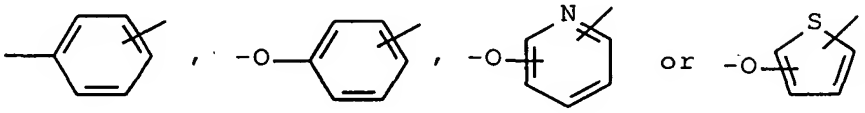
2. A compound of claim 1, wherein





X is bond, -O-, $-OCH_2-$, -S- or $-N(R^7)-$ (in which R^7 is hydrogen or lower alkyl),

Y is bond, $-O-(CH_2)_n-$ (in which n is 1, 2, 3 or 4), $-(CH_2)_m-$ (in which m is 1, 2, 3 or 4),



R^1 is hydrogen or halogen,

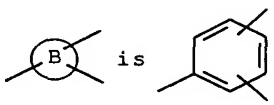
R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

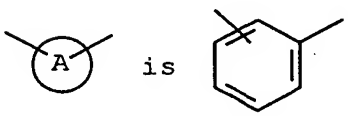
R^5 is hydrogen, halogen, hydroxy or lower alkyl, and

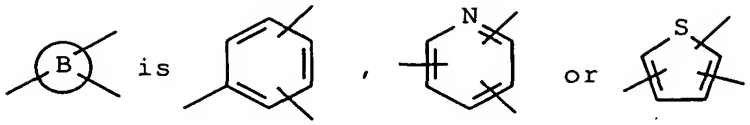
R^6 is hydrogen,

provided that when X is bond, and 

then R^5 is not hydrogen.

3. A compound of claim 2, wherein





X is bond, -O-, $-OCH_2-$, -S- or $-\underset{\underset{R^7}{|}}{N}-$ (in which R^7 is hydrogen or lower alkyl),

Y is bond, $-O-(CH_2)_n-$ (in which n is 1 or 2) or $-(CH_2)_m-$ (in which m is 1 or 2),

R^1 is hydrogen or halogen,

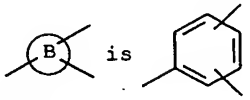
R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

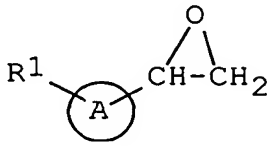
R^5 is hydrogen, halogen, hydroxy or lower alkyl, and

R^6 is hydrogen,

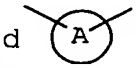
provided that when X is bond, and  then R^5 is not hydrogen.

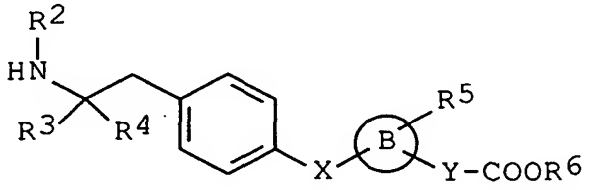
4. A process for preparing a compound of claim 1, or a salt thereof, which comprises,

(i) reacting a compound [II] of the formula:



[II]

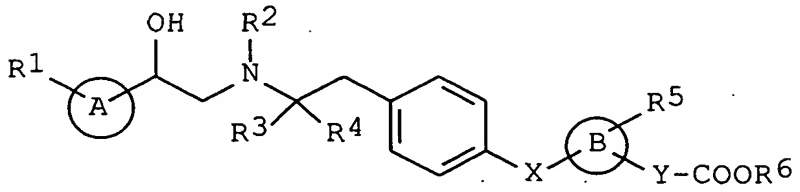
wherein R^1 and  are each as defined in claim 1, with a compound [III] of the formula:



[III]

wherein  , X, Y, R^2, R^3, R^4, R^5 and R^6 are each as defined in claim 1,

or a salt thereof, to give a compound [I] of the formula:

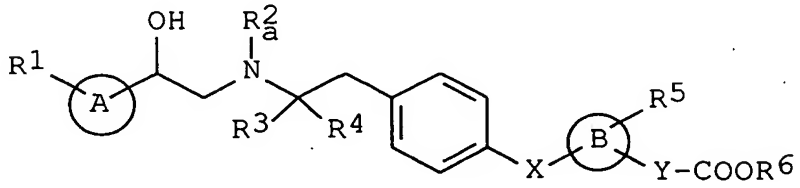


[I]

wherein  ,  , X, Y, R^1, R^2, R^3, R^4, R^5 and R^6 are each as defined in claim 1,

or a salt thereof,

(ii) subjecting a compound [Ia] of the formula:

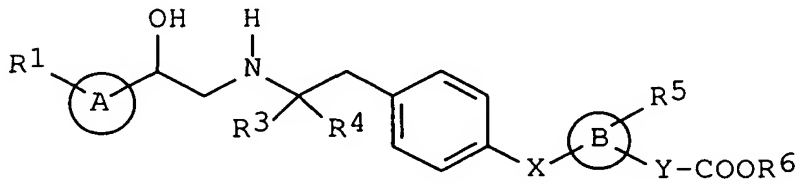


[Ia]

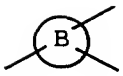
wherein  ,  , X, Y, R^1, R^3, R^4, R^5 and R^6 are each as defined in claim 1, and

R^2_a is an amino protective group,

or a salt thereof, to elimination reaction of the amino protective group, to give a compound [Ib] of the formula:

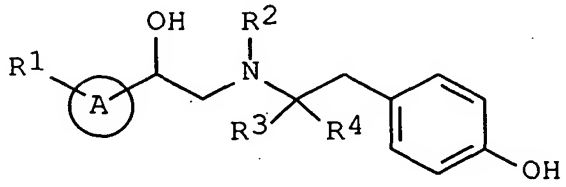


[Ib]

wherein  ,  , X, Y, R^1, R^3, R^4, R^5 and R^6 are each as defined in claim 1,

or a salt thereof,

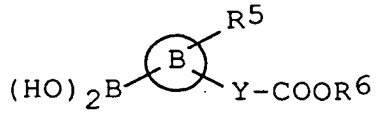
(iii) reacting a compound [IV] of the formula:



[IV]

wherein  , R^1, R^2, R^3 and R^4 are each as defined in claim 1,

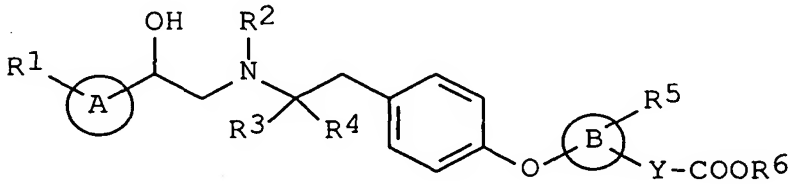
or a salt thereof, with a compound [V] of the formula:



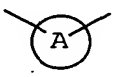
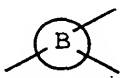
[V]

wherein  , Y, R^5 and R^6 are each as defined in claim 1,

or a salt thereof, to give a compound [Ic] of the formula:

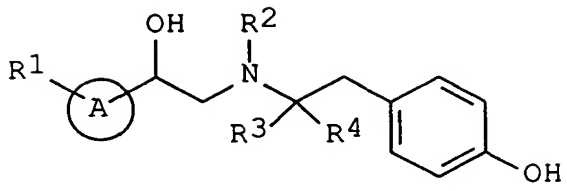


[Ic]

wherein  ,  , Y, R^1, R^2, R^3, R^4, R^5 and R^6 are each as defined in claim 1,

or a salt thereof,

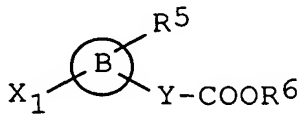
(iv) reacting a compound [IV] of the formula:



[IV]

wherein  , R^1, R^2, R^3 and R^4 are each as defined in claim 1,

or a salt thereof, with a compound [VI] of the formula:

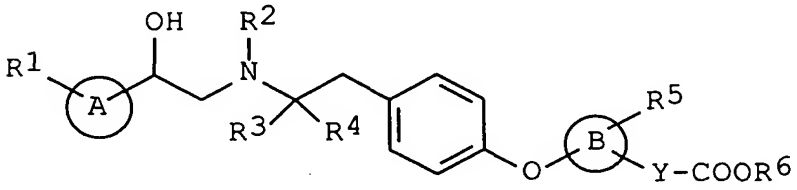


[VI]

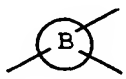
wherein  , Y, R^5 and R^6 are each as defined in claim 1, and

X_1 is a leaving group,

or a salt thereof, to give a compound [Ic] of the formula:

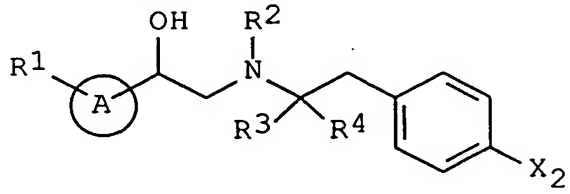


[Ic]

wherein  ,  , Y, R^1, R^2, R^3, R^4, R^5 and R^6 are each as defined in claim 1,

or a salt thereof, and

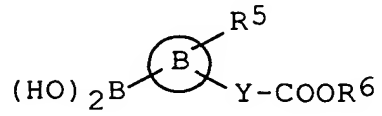
(v) reacting a compound [VII] of the formula:



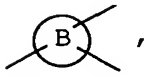
[VII]

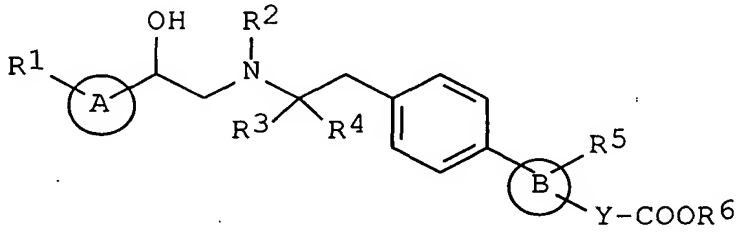
wherein  , R^1, R^2, R^3 and R^4 are each as defined in claim 1,

X_2 is a leaving group,
or a salt thereof, with a compound [V] of the formula:

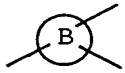


[V]

wherein  , R^5 and R^6 are each as defined in claim 1,
or a salt thereof, to give a compound [Id] of the formula:



[Id]

wherein  ,  , Y, R^1, R^2, R^3, R^4, R^5 and R^6 are each as defined in claim 1,
or a salt thereof.

5. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

6. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

7. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

8. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as selective β_3 adrenergic receptor agonists.

9. A method for the prophylactic and/or the therapeutic treatment of pollakiuria or urinary incontinence which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

DATED this 27th day of June 2002

Fujisawa Pharmaceuticals Pty Ltd

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant